27. (New) A vaccine comprising a ressortant virus comprising the nucleic acid sequence of Claim 25 and a pharmaceutically acceptable carrier.

II. REMARKS

The subject invention is directed to influenza polynucleotide sequences that are useful for the preparation of vaccines and viral vectors. To this end, Applicants have isolated and sequenced a cold-adapted influenza virus. The nucleic acid and amino acid sequences for the eight genes of the cold-adapted influenza virus of this invention are set forth in Sequence Listing Numbers 1 to 20. The nucleic acid and amino acid sequences of the eight genes of the progenitor A/Ann Arbor/6/60 virus are set forth in Sequence Listing Numbers 21 to 41.

The cold-adapted virus of this invention has within it several novel and critical mutations. Reassortant vaccines carrying these mutations have been shown to have the proper level of attenuation, immunogenicity, and non-transmissibility combined with proven genetic stability.

One polynucleotide of this invention codes for the PB2 gene of the cold-adapted virus. The application papers identify the sequence of the PB2 gene of the progenitor influenza virus in Sequence Listing Number 29. (Claim 5). Mutated PB2 has critical differences at nucleotide positions 141, 821 and 1933 as compared to prior art sequence information. The mutated PB2 gene is the subject matter of claim 1 and new claim 25. The difference between the mutated PB2 gene and the same gene of the progenitor strain are described on page 15, line 23 to page 16, line 11 and in Sequence Listing Number 15.

Polynucleotides and reassortant virus containing the mutated PB2 gene are the subject matter of claims 8, 12, 22 and 23 and new claim 27. These claims have been amended herein to more clearly point out this subject matter. Support for the amendments to claims 8, 12, 22 and 23

as well as new claim 27 is found in the application papers on page 4, lines 10 to 21 and lines 32 to 34.

The claims have been further amended herein to provide proper antecedent basis for the term "polynucleotide" in the dependent claims. No new matter has been added by these amendments and entry thereof is respectfully requested.

The subject application is a file wrapper continuation application of U.S. Serial No. 08/082,846. In connection with the prosecution of the parent application, a Final Office Action was issued on June 14, 1995. Applicants responded to this Action on October 13, 1995. Several of the claims were cancel or amended without prejudice or disclaimer in a sincere effort to remove the major issues precluding claim allowance. However, the Examiner did not subsequently allow the case for the reasons set forth in the Advisory Action mailed November 24, 1995. The subject continuation application was filed to continue prosecution of the pending claimed matter.

This Preliminary Amendment is submitted in response to this Advisory Action. On page 1 of the Advisory Action, the Examiner noted that the after Final amendments would not be entered for several reasons. One ground for non-entry as to the addition of new claims 22 and 23 was their alleged lack of antecedent basis for the term "polynucleotide" in the base, independent claim. By this Preliminary Amendment, the independent claims have been amended to provide support for the term "polynucleotide" thereby obviating this ground for rejection.

The Examiner also refused to enter the amendments to the claims on the ground that the addition of the claim elements polynucleotides coding for PB1, PA and M of a cold adapted virus would require further search consideration under 35 U.S.C. § 112, first paragraph.

This amendment to claims 8 and 12 were made in response to the Examiner's rejection appearing on page 7 of the Final Office Action that it appears more than the PB2 gene is required for attenuation. The Examiner opined that the specification fails to provide an enabling

disclosure of how to make polynucleotides coding for PB1, PA and M proteins of a cold adapted virus.

Applicants traverse. The specification provides full polynucleotide sequences for these genes in the sequence listing portion of the specification. Thus, these elements of the claims are fully enabled by the specification.

The Examiner also failed to consider and make of record copies of the art submitted with the prior response. Consideration and entry of this art is requested at this time.

The Examiner also stated that more than the PB2 gene appears to be required for attenuation, citing an article by Snyder et al. The article by Subbarao et al. (1993) Am. Soc. for Micro. Vol.67(12):7223-7228, that mutations in the PB2 gene alone can confer temperature sensitive and attenuated phenotypes. The authors specifically report this finding on page 7227, column 2 of the paper. This is contrary to the teachings of Snyder et al. cited by the Examiner. In addition, in the research reported in Snyder et al., the virus reported therein does not contain the mutations in the PB2 gene that are the mutations present in the claims of this invention and the work reported in Subbarao et al. (1993) id.

Applicants further note that this rejection is improper against new claims 25 and 26 as they are directed to the PB2 gene shown in Sequence Listing 15 *per se* or in combination with additional nucleic acids. The addition of additional genes for attenuation is not required to claim the sequence *per se*.

The Examiner also maintained that the rejection of the claims under 35 U.S.C. § 103, as allegedly obvious in view of the prior art of record on the ground that Applicants have not shown that the mutations present in the PB2 gene (Sequence Listing Number 15) were not an obvious or analogous variant of the prior art PB2 genes. Applicants again traverse this rejection and point the Examiner to the publication of Subbarao et al. (1995) J. Virol. Vol 69(10):5969-5977, previously submitted. Applicants submit this reference to show that sequential addition of

mutations in the PB2 region of influenza conferred sequentially increasing temperature sensitivity and attenuation of the resultant virus.

The preceding amendments place the claims in condition for allowance. Removal of the prior rejection of record is respectfully requested.

III. CONCLUSION

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 29, 1996

Respectfully submitted,

By: _____

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